The present invention relates to the field of therapeutic chemistry and more particularly to the field of hormonal pharmaceutical techniques.

A more precise subject of the invention in new pharmaceutical compositions formed by an estroprogestative combination with a view to the correction of estrogenic deficiencies in natural or artificial menopauses or in order to stop ovulation in women during their period of ovarian activity.

In particular a subject of the invention is an estroprogestative combination, characterized in that it is constituted bu unit doses containing the combination of a progestative and an estrogen, the two components being present simultaneously in each medicinal dose.

This combination is intended to be administered by oral route.

As is known, the life expectancy of women has passed in less than a century from 50 to 80 years, whilst the average age for the onset of menopause has remained unchanged. Therefore, women spend a third of their life in a state of estrogenic deficiency which is the origin of the increase in risk of osteoporosis and cardiovascular illnesses.

Sequential replacement treatment for the menopause cures the climateric symptomology and prevents osteoporosis and the onset of illnesses. It creates artificial cycles which are followed by a withdrawal bleeding. This therapeutic schema quite particularly suits women for whom the menopause is recent but it is not always well accepted in the long term, which in part explains the poorer observance of treatment (DRAPIER FAURE E.; Gynécologie 1992, 43: 271-280).

In order to overcome this drawback, combined combinations have been perfected where the two components are taken simultaneously, the progestive having the effect of permanently opposing the proliferative action of the estrogen on the endometrium,

by creating an atrophy of the endometrium and as a consequence, the absence of withdrawal bleeding (HARGROVE J.T., MAXSON W.S., WENTZ A.C., BURNETT L.S., Obstet Gynecol, 1989, 73: 606-612).

This "no periods" schema more particularly suits women for whom the menopause is already well in the past. It can be prescribed in courses of sequential combinations in order to improve the long-term observance of replacement hormone treatment for the menopause.

The dose of progestative to be used in a combined replacement treatment is in general deduced from that which is usually prescribed in sequential schemata. In the latter the dose chosen is that which gives over the long term less than 1% endometrial hyperplasia when the progestative is administered discontinuously, more than 10 days per cycle, in post-menopasual women under replacement estrogenotherapy (WHITEHEAD et al., J. reprod. Med, 1982, 27: 539-548, PATERSON et al, Br Med J, 1980, 22 March: 822-824).

In the combined treatment, these same progestatives were used at half the dose judged to be effective during a sequential treatment: this is the example of the micronized progesterone, didrogesterone (FOX H., BAAK J., VAN DE WEIJER P., AL-AZZAWI E., PATERSON M., JOHNSON A., MICHELL G., BARLOW D., FRANCIS R., 7th International Congress on the Menopause, Stockholm, 20-24 June 1993, abstr 119) and medroxyprogesterone acetate (BOCANERA R., BEN J., COFONE M., GUINLE I., MAILAND D., SOSA M., POUDES G., ROBERTI A., BISO T., EZPELETA D., PUCHE R., TOZZINI R., 7th International Congress on the Menopause, Stockholm, 20-24 June 1993, abstr 40) which were used at doses of 100, 10 and 5 mg/day respectively, with encouraging results on the clinical and endometrial level.

Among the progestatives, nomegestrol acetate appeared to be one of the most effective. Nomegestrol acetate is a non-androgenic progestative derived from 19-nor progesterone, its use in sequential administration during the menopause at the dose of 5 mg/day, 12 days per cycle, in combination with different types of estrogens, allows endometrial hyperplasia to be prevented as shown by a multicentre study on 150

women for one year (THOMAS J.L., BERNARD A.M., DENIS C., 7th International Congress on the Menopause, Stckholm, 20-24 June 1993, abstr 372).

The absence of hyperplasia was confirmed in a study where the nomegestrol acetate was administered at the same dose, 14 days per cycle, in women treated with percutaneous estradiol (BERNARD A.M. et al. Comparative evaluation of two percutaneous estradiol gels in combination with nomegestrol acetate in hormone replacement therapy. XIV World Congress of Gynecology and Obstetrics, FIGO, Montreal, 24-30 September 1994).

The combined treatment is more often used in a continuous fashion, i.e. without interruption. However some people are in favour of using it in an intermittent fashion, for example 25 days per month (BIRKAUSER M. ET AL; Substitution hormonale: une indication bien posée et des schémas de traitement individuels sont déterminants pour le succès du traitement, Méd. et Hyg., 1995, 53: 1770-1773). The aim of the therapeutic interruption is to remove the inhibition exercised by the progestative on the synthesis of the estradiol and progesterone receptors and in this way to avoid the lowering of receptivity of the hormono-dependant tissues.

The progesterone used according to the present invention is nomegestrol acetate which is active by oral route.

The estrogen used is free or esterified estradiol, or equine conjugated estrogens which are presented according to a formulation which is active by oral route and in particular estradiol valerate.

Nomegestrol acetate and free or esterified estradiol or equine conjugated estrogens are administered in one of the forms which permit administration by oral route: gelatine capsules, capsules, pills, sachets of powder, tablets, coated tablets, sugar-coated tablets etc..

The present invention is characterized in that it is constituted by a new estroprogestative combination, which is active by oral route and administered in a combined manner. A subject of the present invention is also its use in the correction of estrogenic deficiencies, in the prevention of osteoporosis and cardiovascular illnesses in

post-menopausal women, or in stopping ovulation in women during their period of ovarian activity.

The compositions according to the invention based on nomegestrol and free or esterified estradiol or equine conjugated estrogens are administered in a continuous or intermittent fashion, from 21 to 25 days per month.

According to a particular implementation of the invention the compositions contain a quantity of nomegestrol acetate ranging form 1.5 to 3.75 mg and a quantity of free or esterified estradiol or equine conjugated estrogens ranging from 0.5 to 3 mg. Preferably, the optimal formulations contain 2.5 mg of nomegestrol acetate combined with : either 1.5 mg of free estradiol or 2 mg of estradiol ester or 0.625 mg of equine conjugated estrogens, per daily dose.

This combined administration method can have several therapeutic indications. In post-menopausal women, the estroprogestative combination is intended to compensate for the functional disorders brought about by hypoestrogenism of the menopause, while maintaining an atrophy of the endometrium and avoiding in a majority of them the appearance of withdrawal bleeding.

In women during the period of ovarian activity, young or in the years preceding the menopause, the cyclic administration of the hormonal combination is capable of stopping ovulation and of exercising a contraceptive effect insofar as it has been proved that nomegestrol is capable of stopping the ovulation peak of LH and FSH, starting from 1.25 mg/day (BAZIN B. et al, Effect of nomegestrol acetate, a new 19-norprogesterone derivative on pituitary ovarian function in women. Br. J. Obstet. Gynaecol., 1987, 94: 1199-1204). When the hormonal combination is given for a contraceptive purpose, the aim of nomegestrol acetate is to stop ovulation and for the estrogenic compound to compensate for hypoestrogenia and ensure a better control of the cycle.

A subject of the present invention is also a process for obtaining new pharmaceutical compositions.

The obtaining process according to the invention consists of mixing the active ingredients: nomegestrol acetate and free or esterified estradiol or equine conjugated estrogens with one or more pharmaceutically acceptable, non-toxic , inert excipients.

Among the excipients which can be mentioned are binding and solubilizing agents, compression agents, disintegration agents and slip agents.

This mixture can be subjected to direct compression or to several stages of compression in order to form tablets which, if desired, can have their surface protected by a film, by lacquering or coating. The production of tablets by direct compression allows a maximum reduction in the proportion of diluting agents, binding agents, disintegration agents and slip agents.

The production of gelatine capsules can be carried out by mixing the active ingredients with an inert diluant and a slip agent.

The tablets contain, in particular, mass diluting agents such as lactose, sorbitol for direct compression, marketed under the name NEOSORB 60, Palatinite which is a registered trademark for designating an equimolar mixture of the isomer of -D-glucopyranosido 1,6-mannitol and -D-glucopyranosido 1,6-glucitol crystallized with two molecules of water, mannitol, sorbitol or the mixture lactose/PVP sold under the name Ludipress.

The compression binding agents are in general microcrystalline celluloses such as those sold under the name AVICEL PH 101 or AVICEL PH 102.

The polyvinylpyrrolidone plays an important role and facilitates the agglomeration of the powders and the compressibility of the mass. To this end polyvinylpyrrolidones are used with a molecular weight comprised between 10000 and 30000 such as Povidone, Kollidon of a grade comprised between 12 and 30.

The mixture also contains slip or anti-electrostatic agents so that the powder does not agglomerate in the feed hoppers. In this respect, colloidal silicas can be mentioned which are sold under the name AEROSIL 100 or AEROSIL 200.

The mixture also contains disintegration agents which allow disintegration or crumbling which conforms to pharmaceutical standards. There can be mentioned as useful disintegration agents, polymers of cross-linked vinylpyrrolidones such as those sold under the names Polyplasdone or Polyclar AT, carboxymethylamidons such as

those sold under the names Amigel or Explotab, cross-linked carboxymethylcelluloses or croscarmelloses such as the compound sold under the name AC-DI-SOL>

In addition, the preparation contains lubrication agents which facilitate the compression and ejection of the tablet from the tablet compressing machine. There can be mentioned as lubrication agents, glycerol palmitostearate sold under the name Precirol, magnesium stearate, stearic acid or talc.

After compression the tablets can be coated in order to ensure their storage or to facilitate their deglutination.

The coating agents are either of cellulose origin such as cellulose phthalate (Sepifilm, Pharmacoat), or of polyvinyl origin of Sepifilm ECL type, or of saccharose origin such as the sugar for sugar-coating of Sepisperse DR, AS, AP OR K (coloured) type.

The tablets, whether coated or not, can, in addition, be surface or bulk coloured, by plant or synthetic colouring agents (for example chinolin yellow lacquer or E 104).

The proportions of the different constituents varies according to the type of tablet to be produced.

The content of active ingredients can vary from 1.5 to 3.75 mg for nomegestrol acetate and from 0.5 to 3 mg for free or esterified estradiol or for equine conjugated estrogens.

The dilution agents vary from 20 to 75% of the total mass, the slip agents from 0.1 to 2% of the total mass, the compression binding agents vary from 2 to 20%, the polyvinylpyrrolidone from 0.5 to 15%, the disintegration agents vary from 2 to 5.5% for the cross-linked polyvinylpyrrolidone or the carboxymethylamidon, from 2.0 to 3.0% for the croscarmellose.

The quantities of lubricating agents vary as function of the type of agents from 0.1 to 3.0%.

The compositions according to the invention are intended to be administered once per day. However, depending on the therapeutic requirements, administration can be split up (twice per day) or on the other hand, repeated (two tablets per day).

The following examples illustrate the invention. They in no way limit it.

EXAMPLE I

Tablets with 4 mg of active ingredient

Active ingredients:	- estradiol	1.5 mg
	- nomegestrol acetate	2.5 mg
Microcrystalline cellulose		22.4 mg
(marketed under the name AVICEL PH 102)		
Lactose		60 mg
Polyvinylpyrrolidone		8.4 mg
Colloidal silica		1.2 mg
Glycerol palmitostearate		3.6 mg
Colouring agent E.104		0.4 mg

for a tablet completed at an average weight of 100 mg.

EXAMPLE II

Study of the clinical tolerance during two continuous combined schemata of hormone replacement therapy for the menopause

The pilot study is carried out over 24 weeks on two parallel groups subjected to treatments A and C:

Treatment A

- Nomegestrol acetate 2.5 mg/day every day + percutaneous 17β-estradiol 1.5 mg/day every day.
- The nomegestrol acetate is administered in the form of tablets and the percutaneous 17β-estradiol in the form of a gel.

Treatment C

- Nomegestrol acetate 2.5 mg/day every day + estradiol valerate 2 mg/day every day.
- The estradiol valerate is administered in the form of tablets.

The pilot study is intended to evaluate the endometrial clinical tolerance during the use of the two hormone replacement therapy schemata for the menopause so-called "without periods" combining in a continuous combined fashion treatment A or C. The endometrial clinical tolerance is evaluated from the presence or not of occurences of vagina bleeding, their intensity, their frequency, from data acquired from endovaginal echographical examination etc..

Also, another aim of this study is to assess the general clinical tolerance (weight, blood pressure, mammary symptoms), biological tolerance (Formule Numeration Sanguine (blood count), glycemia, cholesterol...), as well as the observance of treatment.

The selection of subjects is carried out as a function of "inclusion" criteria. These criteria are to do:

- with the menopause:

women over 50 years old are included who have had a natural menopause expressed clinically by an amenorrhea greater than 12 months and less than 10 years, the women having had a natural menopause confirmed biologically by quantitative analysis of FSH (Follicle stimulating hormone) and estradiol (i.e. plasmatic FSH $\geq$ 20 IU/l, plasmatic E_2 $\leq$ 0.11 nmol/l).

- with women:

women who have not had hysterectomies are included, whose Quetelet's index (weight in kg/(height in m)^2)is $\leq$ 27, having had regular cycles before the menopause, having never received hormone replacement therapy for the menopause or having had a clinically well-tolerated hormone replacement therapy (absence of abnormal bleeding), interrupted for more than 6 weeks, presenting an endometrial thickness measured by endovaginal echography $\leq$ 5 mm, accepting the idea of hormone replacement therapy for the menopause, who would like a hormone therapy without periods, justifying an estroprogestative hormone therapy for at least 6 months, cooperative: accepting to conform to the requirements of the study, whose psychic and intellectual profile would allow one to suppose a good observance of the treatment, having a mammograph dating from less than a year from the date of inclusion.

At the start of treatment the patients undergo an inclusion consultation (C_1) the purpose of which is to verify that the inclusion criteria have been respected, that the endovaginal echograph is normal and to obtain the written consent of the patient as regards participation.

The intermediate consultation (C_2) takes place between the 9th and 11th week of treatment, the purpose of which is to verify mammary and endometrial clinical tolerance is good as regards the treatment.

Lastly, a final consultation (C_3) takes place during the 24th week of treatment.

The patients who wish to continue the study can receive, for 24 additional weeks, the estroprogestative treatment received during the study according to the same therapeutic schema. The extension of the study thus allows a complete monitoring of the study over 48 weeks.

ANALYSIS OF THE STUDY

RESULTS I

The attached Tables I and II, reveal a difference in terms of the amenorrhea results (i.e. no bleeding from 0 to 24 weeks) and of mammary and/or endometrial tolerance as a function of the estrogen.

TABLE I: Treatment A

Nomegestrol acetate + percutaneous 17β-estradiol

Elapse since menopause ameno/month	Presence of HRT previously	Start of treatment	Duration of treatment weeks	Endometrial thickness before/after mm	COMMENTS
72	no	17.10.94	24 24 ext	2/2	amenorrhea endometrial thickness after 48 weeks of treatment = 2 mm
82	no	04.11.94	24 extension	3/3	amenorrhea
26	yes well tolerated	09.01.95	24 extension	3/3	amenorrhea
108	no	16.01.95	24 extension	1/4	amenorrhea
48	no	13.02.95	24	3/2	1 episode of bleeding at 42 days (a few drops) between the 1st and 6th weeks; breast tension and pain of minimal intensity from the 1st to the 22nd week (7days/week) Extension not effected: did not pick up the treatment kit owing to holidays; following the same treatment outside protocol
24	no	10.03.95	24 extension	2/5	amenorrhea; breast tension and pain of slight intensity from the 6th to the 12th week (7 days/week)
55	yes well tolerated	20.03.95	24 extension	4/8	amenorrhea
27	yes well tolerated	08.05.95	24	3/5	amenorrhea Extension not effected: did not pick up the treatment kit owing to holidays; same treatment outside protocol
90	yes well tolerated	10.04.95	24 extension	4/4	amenorrhea
13	yes well tolerated	03.07.95	24 extension	1 pending	amenorrhea
99	yes well tolerated	24.04.95	24 extension	1/4	amenorrhea
21	yes well tolerated	26.06.95	24 extension	4 pending	amenorrhea
98	?	29.05.95	24 extension	2 pending	amenorrhea
65	yes well tolerated	10.05.95	24 extension	1/3	amenorrhea; 10 episodes (4 days/week) of breast pains of minimal intensity
13	no	12.06.95	stopped at 6	3 not measured	continuous slight bleeding from the 5th week until treatment stopped
38	yes well tolerated	10.07.95	24 extension	2 pending	amenorrhea

EXTENSION = 24 additional weeks of treatment

HRT = hormone replacement therapy

CONCLUSION

Of the 16 patients treated:

- 1 left the study, i.e. 6%
- 15 finished the study after 24 weeks, i.e. 94%
- 13 extensions of treatment (24 additional weeks) 81%

The two extensions which did not take place whee due to reasons which were independent of the treatment, the patients continued the same treatment outside the treatment protocol.

TABLE II: Treatment C

Nomegestrol acetate + estradiol valerate per os

Elapse since menopause ameno/month	Presence of HRT previously	Start of treatment	Duration of treatment weeks	Endometrial thickness before/after mm	COMMENTS
12	no	21.11.94	stopped at 8	4/* *=not measured at the control echo	amenorrhea, breast tension and pain of slight intensity from the 2nd week to the 8th week; STOPPED owing to high abdomino-pelvic tension due to increased size of a sub-serous fibroma: echo before treatment = 37 mm; echo after 8 weeks of treatment = 75 mm
46	yes well tolerated	28.11.94	24 extension	3/6	1 episode of bleeding of 31 days between the 5th and the 9th week (a few drops)
31	yes well tolerated	28.11.94	stopped at 10	2 not measured	amenorrhea, STOPPED for insomnia, nervousness and pain in lower limbs
60	yes well tolerated	30.01.95	24 extension	4/2	amenorrhea, breast tension and pain of slight intensity from the 2nd week of treatment until the 19th week
121	yes well tolerated	08.02.95	stopped at 9	3 not measured	1 episode of bleeding of 16 days of low intensity from the 6th week breast tension of minimal intensity from the 2nd week to the 8th week; STOPPED owing to headaches, night sweats and a blood pressure of 17/10
36	yes well tolerated	06.02.95	24	4*	amenorrhea, 23 episodes of breast tension of high intensity of 7 days/week; extension impossible as estrogen dose reduced due to breast tension
47	yes well tolerated	27.02.95	24 extension	2/2	amenorrhea; 6 episodes of breast tension and pain of slight intensity (2 days/week)
62	no	13.03.95	24 extension	1/4	amenorrhea
74	yes well tolerated	20.03.95	24 extension	4/8	amenorrhea
110	yes well tolerated	08.05.95	stopped at 18	2 not measured	amenorrhea until 12 weeks then 1 episode of bleeding of 41 days until treatment stopped
16	yes well tolerated	22.05.95	24 extension	1 pending	amenorrhea
60	yes well tolerated	12.06.95	stopped at 16	2/3	4 episodes of bleeding of low intensity (6 days/week) 5 episodes of breast pain of medium intensity (6 days/week); STOPPED owing to mastitis and a breast abscess
11	no	19.06.95	24 extension	2 pending	1 episode of bleeding 12 days (a few drops)
38	yes well tolerated	03.07.95	stopped at 4	5 not measured	1 episode of bleeding of 11 days until treatment stopped of low intensity

CONCLUSION

Of the 14 patients treated

- 6 left the study i.e. 43%
- 8 finished the study after 24 weeks, i.e. 57%
- 7 extensions of treatment (24 additional weeks), i.e. 50%

% of amenorrhea (i.e. no occurrence of bleeding for 24 weeks) = 43%

RESULTS II

A - OBSERVANCE

While no significant difference exists between the two groups A and C, a lower number of days when treatment lapsed over all the 24 weeks of the study was observed with treatment A.

B - ENDOMETRIAL CLINICAL TOLERANCE

The most significant absolute percentage of amenorrhea is found in group A, the difference being significant in phase II (13th to 24th week of treatment) As has been described in the literature, the percentage of amenorrhea increases with time; therefore, for group C, it is 35.3% during the first 12 weeks of treatment, and 46.1% during the last 12 weeks.

The attached tables III, IV and V illustrate the results obtained.

AMENORRHEA

Analysis regarding treatment

TABLE III: Phase I / weeks 1 to 12

	TOTAL		GROUP A		GROUP C		P
	N	%	N	%	N	%	
Amenorrhea							
yes	19	37.2 %	9	50 %	6	35.3 %	
no	32	62.7 %	9	50 %	11	64.7 %	0.316
Spotting							
yes	32	62.7 %	9	50 %	11	64.7 %	
no	19	37.2 %	9	50 %	6	35.3 %	0.316

None of the patients suffered from metrorrhagias during phase I

	TOTAL		GROUP A		GROUP C		P
	N	avg±week (min:max)	N	avg±week (min:max)	N	avg±week (min:max)	
Total duration of bleeding (days)	51	9.1±2.1 0:70	18	9.1±4.5 0:70	17	8.9±2.7 0:31	0.412
Average intensity	51	0.8±0.1 0:2	18	0.7±0.2 0:2	17	0.9±0.2 0:2.5	0.446
Number of weeks of bleeding	51	2.1±0.4 0:10	18	1.8±0.7 0:10	17	2.1±0.5 0:7	0.552
Total number of episodes	51	1.2±0.2 0:6	18	1±0.3 0:4	17	1.2±0.4 0:6	0.434

5

TABLE IV: Phase II / weeks 13 to 24

	TOTAL		GROUP A		GROUP C		P
	N	%	N	%	N	%	
Amenorrhea							
yes	20	42.5 %	12	66.7 %	6	46.1 %	
no	27	57.4 %	6	33.3 %	7	53.8 %	0.006
Spotting							
yes	27	57.4 %	6	33.3 %	7	53.8 %	
no	20	42.5 %	12	66.7 %	6	46.1 %	0.006

None of the patients suffered from metrorrhagias during phase II

	TOTAL		GROUP A		GROUP C		P
	N	avg±week (min:max)	N	avg±week (min:max)	N	avg±week (min:max)	
Total duration of bleeding (days)	47	13.9±3.1 0:75	18	6.2±3.3 0:42	13	18.5±7.7 0:75	0.013
Average intensity	47	0.9±0.1 0:2	18	0.6±0.2 0:2.33	13	1.0±0.3 0:2	0.055
Number of weeks of bleeding	47	2.9±0.6 0:12	18	1.3±0.6 0:9	13	3.3±1.2 0:11	0.007
Total number of episodes	47	1.3±0.3 0:7	18	0.6±0.3 0:6	13	1.1±0.5 0:7	0.002

TABLE V

Δ % between C1 and C3	TOTAL		GROUP A		GROUP C		P
	N	avg±week (min:max)	N	avg±week (min:max)	N	avg±week (min:max)	
A.L.A.T.	43	-23.1%±5.2% -88.2%:85.7%	17	-19.0%±3.8% -50%:7.1%	11	-31.2%±13.2% -88.2%:29.4%	0.936
F.S.H.	45	-74.1%±4.9% -98.4%:69.2%	18	-72.2%±5.5% -98%:24.8%	12	-78.2%±9.6% -98.4%:22.8%	0.405
Estradiol (pg/ml)	40	432%±68.5% -54%:1640%	15	567%±118.7% -16%:1320%	10	609%±163.6% -54.3%:1640%	0.036

A.L.A.T. = Alanine Aminotransferase Transaminase

F.S.H. - Follicle Stimulating Hormone

The relative variation in estradiol level is quite important in the two groups (Δ% = 567% in group A and 609% in group c), p = 0.04

Table VI illustrates another study which was carried out. In this other study, it is interesting to note that with nomegestrol acetate, the percentage of patients with absolute amenorrhea (including all forms of estrogenotherapy) is greater from the 3rd month of treatment: 42.5% against 33.3%. In the treatment mentioned above, one must wait until the 12th month of treatment to obtain this percentage of 42% of patients with amenorrhea which was obtained here from 3 months, whilst the populations are comparable in terms of age, weight and length of time since the menopause. In addition, there exists in the previous study, an estrogen effect which is not found in this other study. On the other hand, this study reveals a dosage effect of progestative during the last 9 months of treatment (the lower the dose of progestative the better the cycle is controlled).

Finally, it is interesting to note that no correlation exists between the existence of an amenorrhea at 6 months and the endometrial thickness measured by endovaginal

echography; this thickness varying by +1.6mm on average over 6 months in the 2 treatment groups.

TABLE VI

Characteristics of the patients

	TOTAL		GROUP A		GROUP C		P
	N	avg±week (min:max)	N	avg±week (min:max)	N	avg±week (min:max)	
Age	54	54.9±0.6 45:64	19	53.9±0.8 48:60	17	54.9±1.1 45:63	0.321
Age of amenorrhia (months)	54	56.1±5.0 7:134	19	48.5±7.7 12:108	17	50.7±7.7 11:121	0.309
Weight (kg)	54	60±1.1 42:85	19	61.6±1.2 51:70	17	60.8±2.2 12:76	0.149
Height	54	1.61±0.01 1.47:1.75	19	1.62±0.01 1.57:1.75	17	1.61±0.02 1.47:1.75	0.449
Quetelet's index (kg/m^2)	54	23.1±0.4 17.1:31.2	19	23.3±0.4 19.7:25.6	17	23.5±0.7 17.5:28.7	0.3182
SBP (mmHg)	54	123.9±1.5 100:140	19	127.9±2.5 110:140	17	121.2±2.5 110:140	0.136
DBP (mmHg)	54	74.6±1.2 60:90	19	76.8±2 60:90	17	73.5±2.3 60:90	0.386

H.R.T.	TOTAL		GROUP A		GROUP C		P
	N	%	N	%	N	%	
Previous HRTs							
yes	17	31.5 %	9	47.4 %	14	82.3 %	
no	37	68.5 %	10	52.6 %	8	17.7 %	0.046

HRT = Hormone Replacement Therapy

SBP = Systolic Blood Pressure

DBP = Diasystolic Blood Pressure

Among the contraceptive means most widely and most effectively used, are hormone combinations which act by three different mechanisms, namely, in order of importance:

- inhibition of gonadotropic function, which stops the secretion of FSH and LH from the pituitary and thereby prevents maturation of the ovarian follicles and the occurrence of the ovulatory peak of LH which is essential for oviposition ;
- changes in the secretion and the physicochemical properties of the cervical glairy mucus, making it impermeable to spermatozoa;
- inhibition of the development of the uterine mucosa, which becomes unsuitable for egg-implantation.

In the oestro-progestative combinations used hitherto for contraception, the inhibition of gonadotropic function was due mainly to the oestrogenic fraction consisting of a synthetic oestrogen: ethinyloestradiol. By means of the simultaneous use of 19-nor-testosterone derivatives, the progestative fraction reinforces this inhibition of ovulation, and also ensures the peripheral contraceptive effects on the cervical glairy mucus and the endometrium.

However, the use of the oestro-progestative contraceptive combinations currently available has major drawbacks.

Ethinyloestradiol has a very strong impact on liver function; this is reflected essentially by disorders in the synthesis of clotting factors and by abnomalies in the lipid profile of the plasma (Bonnar, et al., 1987; Meade, 1988; Lindberg et al., 1989; von Shoultz et al., 1989; Daly and Bonnar, 1990; Burkman, 1997; Spitzer, 1997). Consequently, the use of oestro-progestative contraceptives is problematic in at-risk

women (women suffering from circulatory disorders, women in the perimenopause, women who smoke, etc.). This impact is all the more pronounced since the deleterious effect of ethinyloestradiol can be further increased by the progestative fraction on account of a residual androgenic activity which is often present (Bonnar, 1987; Sabra and Bonnar, 1983; Bonnar et al., 1987).

The progestative fraction of the oestro-progestative contraceptives currently available usually consists of a 19-nor-testosterone derivative which, like ethinyloestradiol, has a negative impact on liver function, the lipid profile and blood vessels. Although this has not been demonstrated definitively, the most modern 19-nor-testosterone derivatives, known as third generation progestatives, are suspected of inducing an increase in thromboembolic accidents (O'Brien, 1999).

To escape the drawbacks of ethinyloestradiol, 19-nor-testosterone derivatives are occasionally used alone in contraception, in two different modes:

- either at low doses, and in this case the contraceptive action is ensured by the peripheral effects of the progestative agent; the reason for this is that the inhibition of ovulation is not constant, since the low doses of progestative agent very often allow the development of ovarian follicles and, in certain cases, an increase in the endogenous secretion of oestradiol;
- or at high doses, so as to unequivocally inhibit ovulation, but at the risk of creating a hypooestrogenia, thus limiting their use in young women.

In summary, it appears to be very useful to have available an oestro-progestative combination which is at least as effective as those currently available, but which is free of their harmful side effects.

To do this, it was easy to do the following:

- Replace ethinyloestradiol (EE) with the hormone secreted by the ovaries, 17beta-oestradiol (E2), which is much less toxic than EE (Buckman et al., 1980; Bergink et al., 1981; Lindberg et al., 1989) but is weakly anti-gonadotropic (Hirvonen, 1995). Many attempts have been made, but none has resulted in a product made available to women. In general, the anti-ovulatory effect was clearly obtained, but the many failures were due, in most cases, to poor control of the menstrual cycle with the appearance of spotting and intermenstrual bleeding which made the method unacceptable.

Thus, combinations of natural oestrogens with desogestrel (Wenzl, 1993; Kivinen and Saure, 1996; Csemicsky et al., 1996), with cyproterone acetate (Hirvonen et al., 1988; Hirvonen et al., 1995), with norethisterone (Astedt et al., 1977; World Health Organization, 1980; Serup et al., 1981) were found to be contraceptive, but the intermenstrual bleeding, spotting and poor quality of the periods were unacceptable. For some, the reasons for these failures lay in an insufficient oestrogenic stimulation on account of the poor bioavailability of oestradiol or esters thereof; the excessively intense progestative effect led to a partial inhibition of endometrial proliferation and thus to anarchic bleeding (Hirvonen et al., 1995; Csemicsky et al., 1996). Only one combination gave satisfactory results in terms of controlling the menstrual cycle; this is the combination of oestradiol valerate and dienogest (Oettel et al., 1999; Hoffman et al., 1999). According to these authors, the positive results were thought to be due to a strong dissociation between central activity (anti-ovulatory activity) and peripheral activity (endometrial activity) to the benefit of this latter activity for dienogest. In summary, all of the data published show that the result depends closely on the anti-gonadotropic effect of the progestative agent, the

bioavailability of oestradiol or derivatives thereof in the formulation used and an optimum ratio between the oestrogenic and progestative stimulations.

- Replace the 19-nor-testosterone derivative with a highly anti-gonadotropic synthetic progestative agent which is known not to have any impact on liver function, sugar-lipid metabolism or clotting factors.

Contraceptive effect of the nomegestrol acetate/ oestradiol combination

The present invention relates to a novel oral contraceptive formulation for women of child-bearing age (young or perimenopausal); this formulation being based on the combination of :

1. a synthetic progestative agent which is free from any metabolic side effects, nomegestrol or esters thereof, whose anti-gonadotropic effect is found, unexpectedly, to be potentiated by oestradiol or esters thereof;

2. oestradiol, or a derivative thereof (esters or ethers), to compensate for the hypooestrogenia induced by the progestative agent administered over a prolonged period during the cycle;

3. and the use of an optimum weight ratio between the oestrogenic fraction and the progestative fraction, to ensure good control of the menstrual cycle.

The oestrogenic component involves oestradiol or an ester or an ether thereof, such as, for example, the valerate, benzoate, enanthate, etc., the doses used being calculated as oestradiol equivalents. The doses range from 0.3 mg to 3 mg per day with a preference for a range from 0.5 mg to 2 mg per day. According to the literature data (Hirvonen, 1995), a dose

of 4 mg is needed to ensure the inhibition of ovulation, but they correspond to the doses used to compensate for hypooestrogenic states. For example, in menopausal women, the dose recommended to compensate for hypooestrogenic states is about 1.5 mg.

The progestative component includes nomegestrol or an ester thereof. Nomegestrol acetate will preferably be used. The range of doses is between 0.1 and 2.5 mg per day and preferably between 0.1 and 1.25 mg per day and more preferably between 0.3 and 1.25 mg / day. At these very low doses, the nomegestrol acetate combined with oestradiol inhibits ovulation and follicle maturation in 100% of cases when the two active principles are administered together from the 1st to the 21st day of the cycle, with acceptable frequencies of deprivational haemorrhage and intermenstrual bleeding.

The range of the weight ratio of the oestradiol doses to the nomegestrol acetate doses extends from about 0.5 to 5 and this ratio is preferably between about 1 and 3.

The combination of nomegestrol acetate and oestradiol is administered daily, at the same dose, from the 1st day of the cycle, for a period which may range from 21 to 28 days. Next, the women receive a placebo tablet daily for the period of time required to complete the 28-day cycle (0 to 7 days).

Nomegestrol acetate is a powerful, orally-active progestative agent which has a novel pharmacological profile:

- like 19-nor-testosterone derivatives, nomegestrol acetate bears high anti-gonadotropic activity but, unlike these 19-nor-testosterone derivatives, it does not display any residual androgenic or oestrogenic activity and it has a strong anti-oestrogen activity.

- like 17alpha-hydroxyprogesterone derivatives, it has a pure pharmacological profile, but, unlike the above derivatives, it has a powerful anti-gonadotropic effect.

It belongs to the category of progestative agents known as hybrids (Oettel et al., 1999) which do not bear deleterious metabolic effects on account of the absence of the 17α-ethinyl function, and which combine the advantages of progesterone derivatives with those of the more modern 19-nor-testosterone derivatives.

A clinical trial similar to the Kaufmann's trial, made it possible to show that the endometrial conversion is obtained with a daily dose of 1 mg of nomegestrol acetate, i.e. 10 mg for the entire cycle. It has previously been shown (Bazin et al., 1987) that the inhibition of ovulation and of follicle development were obtained in women with a daily dose of 2.5 mg of nomegestrol acetate. The ratio of the ovulation-inhibiting activity in women (in mg/day) to the endometrial luteinizing activity (in mg/cycle) as defined by Neumann (1977) is thus in the order of 0.2, i.e. close to those of cyproterone acetate and chlormadinone acetate; this indicates a strong central activity (Oettel et al., 1999). In this sense, it clearly differs from dienogest, whose activity is disequilibrated to the benefit of the peripheral activity. Consequently, the results observed with an oestradiol valerate/dienogest contraceptive combination do not in any way suggest and do not make obvious the results observed with the oestradiol/nomegestrol acetate combination according to the invention.

Study of the anti-ovulatory power of the nomegestrol acetate/oestradiol combination shows an unexpected potentiation of the anti-gonadotropic effects of nomegestrol acetate by oestradiol, since the inhibition of ovulation and

of follicle development are obtained with a low dose, in the order of 0.625 mg. This results cannot result from an anti-gonadotropic effect of oestradiol, nor even from an addition of effects between the two active principles since the doses of oestradiol used are very much lower than the doses known to inhibit ovulation (Hirvonen et al., 1995). Consequently, this unexpected observation is a sign of a real innovation, since it allows the use of lower doses of progestative agent and thus better tolerance; it differs from the subject of French Patent 2,754,179 (to the Applicant), in which the range of nomegestrol acetate doses could extend from 1.5 to 5 mg.

The present invention thus relates to an oestro-progestative agent administered in single-stage mode from the 1st day of the cycle for 21 to 28 days. It differs from the claims of many patents which describe the combination of oestradiol or of an oestradiol ester administered in multi-stage modes with modified doses of oestrogenic and/or of the progestative agent from one stage to another and, even occasionally, a change of the progestative agent from one stage to another. Mention should be made in this respect, for example, of patents EP 770338, WO 9741868, WO 9909993, WO 9835682, WO US9817288, WO 9602486, WO 9707074, WO 9707083, WO 9707084, WO 9707085, WO 9707089, WO 9712785, WO 9712785, WO 9712786, WO 9712787, WO 9712788, WO 9712789, WO 23228, WO 9741868, WO 9913882, EP 491,438, EP 491,415, WO 9004330, EP 3092263, US 4628051, EP 0911029 A2, EP 0770388 A1 and DE 3229612, as well as the publications by Hirvonen et al. (1988, 1995) which describe a two-stage contraceptive method with the oestradiol valerate/cyproterone acetate combination or that by Hoffmann et al. (1988) which describes a two-stage contraceptive method with the oestradiol valerate/dienogest combination.

The present invention includes a method of contraception combining 17β-oestradiol or an ester or ether thereof and

nomegestrol or one of the esters thereof, preferably nomegestrol acetate. This method of contraception is novel with respect to the patents and publications devoted to oestro-progestative combinations of oestradiol (or of one of the esters or ethers thereof) and of a progestative agent administered in single-stage mode, since the literature as a whole shows that the overall clinical result is entirely dependent on the nature of the progestative agent used, its pharmacological profile, its effects on the hypothalamo-hypophyseal axis of the "central" power/"peripheral" power ratio and the ratio of oestrogenic and progestative activity. For these reasons, the single-stage methods of contraception described in some patents, such as, for example, WO 95/17194, WO 99/12531 and EP 0,253,607, and in some publications, such as, for example, those which deal with norethisterone/oestradiol combinations (Astedt et al., 1977; Task force on oral contraception, 1980; Serup et al., 1981), those which deal with desogestrel/oestradiol combinations (Wenzl et al., 1993; Csemicsky et al., 1996) or combinations of dienogest and oestradiol (Hoffmann et al., 1998) cannot be applied to the combination of nomegestrol acetate/oestradiol since they are validated only for the oestrogen and the progestative agent claimed. Added to this is the fact that the potentiation observed between oestradiol and nomegestrol acetate renders any extrapolation of doses from the pharmacological profile unnecessary. Furthermore, nomegestrol acetate is never cited as a progestative agent which can be used. Patents EP 309,263 and WO 90/04330 cited the possibility of using 17alpha-19-nor-progesterone and esters thereof, but it should be pointed out, on the one hand, that nomegestrol acetate is not a 17alpha-19-nor-progesterone ester, and, on the other hand, that 17alpha-19-nor-progesterone esters bear antidiuretic properties which render them unsuitable for use in women (Paris et al., 1987).

A preferred composition will be one which contains 0.312 mg of nomegestrol acetate per 1 mg of oestradiol or 0.625 mg of nomegestrol acetate and 1 mg of oestradiol or 0.625 mg of nomegestrol acetate and 1.5 mg of oestradiol or alternatively 0.625 mg of nomegestrol acetate and 2 mg of oestradiol.

The pharmaceutical compositions according to the invention are those which are suitable for the digestive route, in particular in the form of plain or film-coated tablets, sugar-coated tablets, gelatine capsules, wafer capsules, pills, cachets or powders, which may or may not contain flavourings. They contain a diluent and/or a filling substance and/or a tabletting adjuvant and/or a lubricant and/or a splitting agent. Film-forming agents which may be mentioned are hydroxypropylmethylcellulose (Hypromellose) and cellulose acetophthalate.

Binders which may be used are polyvinylpyrrolidone, carboxymethylcellulose, crosslinked carboxymethylcellulose, microcrystalline cellulose, ethylcellulose, hydroxyethylcellulose or a starch which may or may not have been chemically modified. Filling substances which may be mentioned are calcium carbonate, magnesium carbonate, magnesium phosphate, clays, zeolites, infusorial earth, etc. Tabletting adjuvants which may be mentioned are powdered sugar or lactose. Lubricants which may be mentioned are talc, calcium stearate, magnesium stearate and colloidal silica. Splitting agents which may be mentioned are mannitol, carboxymethylstarch and polyvinylpyrrolidone.

In general, the weight of the compositions according to the invention ranges between 40 and 100 mg and the composition contains from 80 to 99% of diluents and excipients per 1 to 20% of active principles.

Nomegestrol acetate and oestradiol can be administered simultaneously, combined in a single formulation, or, on the contrary, may be present in two pharmaceutical forms to be ingested successively or simultaneously.

The daily dosage will be 1 or 2 intakes and the duration of the treatment will be exerted throughout the entire month. In total, the mean monthly dose of nomegestrol acetate will range from 8 mg to 75 mg. The doses are fully tolerated.

EXAMPLE I: examples of formulations

The combination of nomegestrol acetate and oestradiol is presented in the form of plain or film-coated tablets.

In these compositions, oestradiol is advantageously introduced into the final mixture in the form of a premix containing from 2 to 5% of oestradiol in povidone (10 to 25%) and lactose (qs 100%), such as, for example:

FORMULATIONS	IN MG/1 TABLET	IN %
Oestradiol	1.00	2.50
Povidone	6.00	15.00
Lactose	33.00	82.50
Isopropyl alcohol	# 6.14	# 15.35
Demineralized water	# 1.06	# 2.67
TOTAL ON DRY	**40.00**	**100.00**

This premix is introduced into the final mixture in order to obtain a tablet by direct tabletting.

The plain finished tablets generally weigh from 60 to 90 mg and have the overall formulation below:

FORMULATIONS OF THE PLAIN TABLETS

Composition

	in mg/ tablet
- Oestradiol premix qs	0.5 to 1.5
- Nomegestrol acetate	0.300 to 2.500
- Colloidal silica	0.300 to 1.500
- Crospovidone	2.500 to 5.000
- Lactose	4.000 to 40.000
- Cellulose	6.000 to 40.000
- Stearic acid	0.900 to 3.00
- Talc	0.450 to 1.500 mg

By way of example, mention may be made of tablets weighing 90 mg and having the formulation below:

Examples of formulations (UF = unit formulation) 90 mg tablets

FORMULATIONS	**UF mg/1 90 mg tablet**	**UF %**
Premix containing 2.5% oestradiol	40.000	44.45
Nomegestrol acetate	0.300	0.33
Colloidal silica (Aerosil 200)	0.495	0.55
Crospovidone (Polyplasdone XL)	3.240	3.60
Lactose	26.000	28.89
Microcrystalline cellulose (Avicel PH 101)	17.265	19.18
Stearic acid AC68/50VG	1.800	2.00
Talc	0.900	1.00
TOTAL	**90.000**	**100.00**

FORMULATIONS	UF mg/1 90 mg tablet	UF %
Premix containing 2.5% oestradiol	40.000	44.45
Nomegestrol acetate	2.500	2.77
Colloidal silica (Aerosil 200)	0.495	0.55
Crospovidone (Polyplasdone XL)	3.240	3.60
Lactose	24.900	27.67
Microcrystalline cellulose (Avicel PH 101)	16.165	17.96
Stearic acid AC68/50VG	1.800	2.00
Talc	0.900	1.00
TOTAL	**90.000**	**100.00**

FORMULATIONS	UF mg/1 90 mg tablet	UF %
Premix containing 2.5% oestradiol	60.000	66.67
Nomegestrol acetate	0.300	2.77
Colloidal silica (Aerosil 200)	0.495	0.55
Crospovidone (Polyplasdone XL)	3.240	3.60
Lactose	12.215	8.91
Microcrystalline cellulose (Avicel PH 101)	13.050	14.50
Stearic acid AC68/50VG	1.800	2.00
Talc	0.900	1.00
TOTAL	**90.000**	**100.00**

FORMULATIONS	UF mg/1 90 mg tablet	UF %
Premix containing 2.5% oestradiol	60.000	66.67
Nomegestrol acetate	0.625	0.69
Kollidon 25	9.000	10.00
Colloidal silica (Aerosil 200)	0.495	0.55
Crospovidone (Polyplasdone XL)	3.240	3.60
Microcrystalline cellulose (Avicel PH 101)	13.050	14.50
Stearic acid AC68/50VG	1.800	2.00
Talc	0.900	1.00
Lactose	0.890	0.99
TOTAL	**90.000**	**100.00**

Plain tablets weighing 60 mg and having the formula below, can also be prepared:

Examples of formulations (UF = unit formulation) 60 mg tablets

FORMULATIONS	UF mg/1 60 mg tablet	UF %
Premix containing 4.0% oestradiol	25.000	41.67
Nomegestrol acetate	0.300	0.50
Colloidal silica (Aerosil 200)	0.324	0.54
Crospovidone (Polyplasdone XL)	3.000	5.00
Lactose	16.076	26.779
Microcrystalline cellulose (Avicel PH 101)	13.500	22.50
Stearic acid AC68/50VG	1.200	2.00
Talc	0.600	1.00
TOTAL	**60.000**	**100.00**

FORMULATIONS	UF mg/1 60 mg tablet	UF %
Premix containing 4.0% oestradiol	25.000	41.67
Nomegestrol acetate	2.5000	4.17
Colloidal silica (Aerosil 200)	0.324	0.54
Crospovidone (Polyplasdone XL)	3.000	5.00
Lactose	14.976	24.96
Microcrystalline cellulose (Avicel PH 101)	12.400	20.66
Stearic acid AC68/50VG	1.200	2.00
Talc	0.600	1.00
TOTAL	**60.000**	**100.00**

FORMULATIONS	UF mg/1 60 mg tablet	UF %
Premix containing 4.0% oestradiol	37.500	62.50
Nomegestrol acetate	0.625	1.04
Kollidon 25	7.000	11.67
Colloidal silica (Aerosil 200)	0.324	0.54
Crospovidone (Polyplasdone XL)	3.000	5.00
Microcrystalline cellulose (Avicel PH 101)	8.213	13.69
Stearic acid AC68/50VG	1.200	2.00
Talc	0.600	1.00
Lactose	1.538	2.56
TOTAL	**60.000**	**100.00**

FORMULATIONS	UF mg/1 60 mg tablet	UF %
Premix containing 4.0% oestradiol	37.500	62.50
Nomegestrol acetate	0.300	4.17
Colloidal silica (Aerosil 200)	0.324	0.54
Crospovidone (Polyplasdone XL)	3.000	5.00
Lactose	7.076	16.08
Microcrystalline cellulose (Avicel PH 101)	10.000	8.71
Stearic acid AC68/50VG	1.200	2.00
Talc	0.600	1.00
TOTAL	**60.000**	**100.00**

FORMULATIONS	UF mg/1 60 mg tablet	UF %
Premix containing 4.0% oestradiol	25.000	41.67
Nomegestrol acetate	2.500	4.17
Colloidal silica (Aerosil 200)	0.324	0.54
Crospovidone (Polyplasdone XL)	3.000	5.00
Lactose	14.976	24.96
Microcrystalline cellulose (Avicel PH 101)	12.400	20.66
Stearic acid AC68/50VG	1.200	2.00
Talc	0.600	1.00
TOTAL	**60.000**	**100.00**

These tablets can be film-coated with, for example:

- film-forming agents based on polyvinyl alcohol, of the type OPADRY PVA "moisture barrier" (polyvinyl alcohol, titanium dioxide, purified talc, lecithin, xanthan gum, pigments, lacquers),

or

- film-forming agents based on cellulose, of the type SEPIFILM L.P. [HPMC (hydroxypropylmethyl cellulose)], microcrystalline cellulose, stearic acid, pigments, lacquers.

EXAMPLE II: potentiation of the anti-gonadotropic effect of nomegestrol acetate with oestradiol

The anti-ovulatory action of the oestradiol/nomegestrol acetate combination was evaluated in a randomized double-blind study on 38 female volunteers, in good health, aged 18 to 35, in the period of ovarian activity, for whom it was checked beforehand, by means of an assay of the progesterone in the plasma and the establishment of a temperature curve, that they had ovulatory menstrual cycles.

The women were monitored for two consecutive cycles: the first was a control cycle without treatment; during the following cycle (cycle under treatment), they received a hormonal treatment administered orally daily from the 1st to the 21st day of the cycle.

According to the randomization:

- 9 women received 1.5 mg of oestradiol + 0.625 mg of nomegestrol acetate (group A),
- 10 others received 1.5 mg of oestradiol + 1.25 mg of nomegestrol acetate (group B),
- another 10 received 1.5 mg of oestradiol + 2.5 mg of nomegestrol acetate (group C),
- and the other 9 were treated with nomegestrol acetate alone at a dose of 2.5 mg (group D).

During the control cycle, the hormonal parameters were not significantively different among the four groups.

Table I indicates the mean concentrations observed for each hormonal parameter in the course of the 21 days of treatment.

In all the women, and irrespective of the doses administered, the cycles under treatment were all anovulatory, with a disappearance of the mid-cycle peak of LH and a progesterone level in the plasma of less than 1 ng/ml.

Comparison of the hormonal parameters in groups C and D made it possible to show that the combination of oestradiol with nomegestrol acetate not only significantly increased the oestradiol level in the plasma, but also reinforced the anti-gonadotropic effect of the progestative agent. Specifically, in the presence of oestradiol, the LH and FSH levels were found to be statistically lower than those observed when nomegestrol acetate was administered alone.

When nomegestrol acetate is combined with oestradiol, it exerts anti-gonadotropic effects, even at low doses (0.625 and 1.25 mg), since the hormonal parameters were not found to be significantively different in groups A, B and C.

This synergistic effect of oestradiol is confirmed by comparing the results of this study with those of another clinical trial performed according to the same methodology, but with the progestative agent alone. This comparison in fact shows that, at a dose of 1.25 mg of nomegestrol acetate, the addition of oestradiol has no appreciable influence on the levels of progesterone and of gonadotrophins (LH and FSH) in the plasma. On the other hand, the addition of oestradiol lowers the plasmatic levels of oestradiol, assayed 24 hours after taking the medicinal product, by about 300%; this parameter is a good reflection of the endogenous secretion of the ovaries (*Table II*).

It is known that nomegestrol acetate given alone at a rate of 1.25 mg per day abolishes ovulation and prevents the formation of the corpus luteum, while at the same time resulting in an increase in the level of oestradiol in the plasma, which is evidence of follicle development without ovulation, as is encountered with the progestative micropill.

This study has thus shown that the addition of a dose of oestradiol, which is insufficient to block ovulation by itself, reinforces the anti-ovulatory effects of the progestative agent and also inhibits folliculogenesis, and maintains oestradiol levels markedly below 100 pg/ml an appreciable time after taking the medicinal product. It is thus possible to observe anti-ovulatory effects with lower doses of nomegestrol acetate than those initially used when it is combined with oestradiol; this confirms, in the new study, the results obtained with 0.625 mg of nomegestrol acetate (NOMAC) per day, combined with oestradiol.

In this study, the reading of the genital bleeding allows to evaluate the effect of the oestradiol/nomegestrol acetate combination on the cycle. In all of the women treated with the oestro-progestative combination, it was thus observed that the duration of the cycle did not exceed 1 month in 50% of cases, that spotting was totally absent from one woman in two and that the deprivational haemorrhage after stopping the treatment was on average 5.4 days and did not exceed 7 days in 86% of the women. These data did not differ among the groups. As regards the first treatment cycle, they reflect a satisfactory level of tolerance; in point of fact, it is known that the quality of the cycles obtained with this type of combination improves after a few cycles of treatment.

Table I: Mean concentrations in the plasma (m ± sem) of gonadotrophins (LH and FSH) and of ovarian steroids (oestradiol and progesterone) in the course of a cycle under treatment with 3 oestradiol /nomegestrol acetate (E2/ NOMAC) combinations. Comparison with the treatment with nomegestrol acetate alone

Hormonal Parameter	Group A (n=9) 1.5 mg E2 + 0.625 mg NOMAC	Group B (n=10) 1.5 mg E2 + 1.25 mg NOMAC	Group C (n=10) 1.5 mg E2 + 2.5 mg NOMAC	Group D (n=9) 2.5 mg NOMAC	p (ANOVA)	
					Comparison A, B, C	Comparison C and D
LH (mIU/ml)	4.1 ± 0.51	3.0 ± 0.51	2.7 ± 0.49	5.6 ± 0.62	0.135	0.002
FSH (mIU/ml)	6.2 ± 0.42	6.6 ± 0.52	5.4 ± 0.75	7.6 ± 0.28	0.318	0.019
Progesterone ng/ml	0.11 ± 0.031	0.07 ± 0.024	0.03 ± 0.009	0.07 ± 0.014	0.068	0.056
Oestradiol pg/ml	62.0 ± 7.90	57.6 ± 4.53	47.2 ± 5.61	31.9 ± 3.91	0.225	0.043

Table II: Mean concentrations (m ± sem) of gonadotrophins (LH and FSH) and of oestradiol in the plasma with 1.25 mg of nomegestrol acetate combined or not combined with oestradiol.

Hormonal Parameter	Cycle	NOMAC 1.25 mg (n=3)[1]	NOMAC 1.25 + E2 1.5 mg (n=10)[2]
LH (mIU/ml)	Control	4.5 (4.0-5.0)	7.1 ± 0.82
	Treated	3.1 (2.6-3.7)	3.0 ± 0.51
FSH (mIU/ml)	Control	4.3 (4.0-4.5)	6.6 ± 0.28
	Treated	3.3 (2.5-4.2)	6.9 ± 0.48
Oestradiol pg/ml	Control	112.0 (64.8-203.8)	132.9 ± 10.57
	Treated	158.8 (99.5-201.7)	47.2 ± 5.61

E2 = oestradiol; NOMAC = nomegestrol acetate

[1] = m (breadth); [2] = m ± sem

EXAMPLE III : effect of the nomegestrol acetate /oestradiol combination on the endometrium

A study was carried out to test the effects on the endometrium of several doses of nomegestrol acetate combined with an oral dose of oestradiol equivalent to 1.5 mg.

In the course of this study, 179 women who had been menopausal for at least 3 years received continuously every day 2 mg of oestradiol valerate combined with four different doses of nomegestrol acetate: 5 mg (n=47), 2.5 mg (n=42), 1.25 mg (n=43) and 0.625 mg (n=47).

The effect of these four combinations on the endometrium was evaluated by measuring the thickness of the endometrium by endovaginal echography and by carrying out a biopsy on the endometrium before and after the treatment.

Table IV indicates the results of the echographic examination. At the end of the treatment, the mean thickness of the endometrium remains less than or in the order of 4 mm. The increase in thickness under treatment is 0.39 mm on average with the lowest dose of nomegestrol acetate (0.625 mg/day). It increases slightly as the dose increases, but remains less than 1.5 mm with 2.5 mg/day.

The biopsies examined at the end of the study (*Table V*) revealed no proliferative or hyperplasic appearance of the uterine mucosa after 6 months of treatment. The

greatest number of atrophic endometria were observed with the lowest doses of nomegestrol acetate.

These results indicate that low doses of nomegestrol acetate administered continuously with oestradiol are capable of sufficiently impregnating the endometrium and of ultimately preventing the growth of the uterine mucosa.

Table III: Endometrial thickness after 6 months of treatment with several continuous combined combinations based on oestradiol (2 mg of oestradiol valerate) and nomegestrol acetate (NOMAC) at several doses

Doses of NOMAC (mg/day)	0.625 (n = 35)	1.25 (n = 33)	2.5 (n = 34)	5 (n = 41)
Mean thickness at the end of treatment (mm)	3.18 (1.65)	4.05 (3.75)	3.93 (2.10)	3.83 (2.72)
Mean increase in thickness under treatment (mm)	0.39 (1.67)	1.12 (3.67)	1.36 (1.54)	1.57 (2.39)

( ) = standard deviation

Table IV: Histological appearance of the endometrium after 6 months of treatment with several continuous combined combinations based on oestradiol (2 mg of oestradiol valerate) and nomegestrol acetate (NOMAC) at several doses

Doses of NOMAC (mg/day)	0.625 (n = 32)	1.25 (n = 33)	2.5 (n = 34)	5 (n = 40)
Absence of endometrium	5 (15.6)	10 (30.3)	3 (8.8)	3 (7.5)
Atrophic endometrium	19 (59.4)	10 (30.3)	8 (23.5)	3 (7.5)
Secretory endometrium	8 (25.0)	12 (36.4)	22 (64.7)	34 (85.0)
Polyp	0	1 (3.0)	1(2.9)	0

( ) = percentage

No endometrium was proliferative or hyperplasic